25. (Amended) A prosthesis comprising fully crosslinked tissue having an exogenous polypeptide growth factor associated therewith.

29. (Twice Amended) A prosthesis for a human patient comprising allograft or xenograft tissue having a polypeptide growth factor associated therewith by a biologic adhesive, covalent bonding using crosslinking agents comprising reactive functional groups, antibody-antigen associations, specific binding protein-receptor associations or enzyme substrate associations, said polypeptide growth factors being effective to stimulate the affiliation of viable cells with said tissue.

## REMARKS

Claims 1, 2, 4-11, 14, 15 and 21-29 are pending. By this Amendment, claims 14, 25 and 29 are amended to more particularly point out Applicants' claimed invention. The amendment of claim 14 is supported by the specification, for example, at page 4, lines 6-9. The amendment of claim 25 is supported by the specification, for example, at page 8, lines 12-18, page 20, lines 30-32 and page 21, lines 12-18. The amendment of claim 29 is supported by the specification, for example, at page 14, lines 23-28. Applicants have amended claims 25 and 29 to clarify the claim scope and do not believe that the scope of these claims has changed from the previously intended scope. No new matter is introduced by the amendments.

Applicants respectfully request reconsideration of the pending rejections based on the following comments.

Double Patenting

The Examiner provisionally rejected claims 1, 2, 4-6, 9-11, 14 and 21-29 under the judicial doctrine of obviousness-type double patenting as being unpatentable over claims 1, 3, 4, 8-11, 13 and 15 of copending Application No. 09/186,810. Applicants will consider filing a terminal disclaimer once the claims have been found otherwise patentable.

Rejections Under 35 U.S.C. §112, First Paragraph

The Examiner rejected claim 29 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. In particular, the Examiner asserts that the language "plurality of reactive functional groups" lacks clear original support for the entire range. The Examiner indicated that the specification only supports "two reactive groups." Applicants respectfully request reconsideration based on the following comments.

While Applicants maintain that a person of ordinary skill in the art recognizes that a crosslinking agent inherently includes a plurality of functional groups, Applicants have deleted a portion of the language cited by the Examiner. By deleting the language, Applicants rely on the meaning of "crosslinking agent" to a person of ordinary skill in the art to convey the same claim scope. In view of the amendment, Applicants respectfully request withdrawal of the rejection of claim 29 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Rejections Under 35 U.S.C. §112, Second Paragraph

The Examiner rejected claim 29 under 35 U.S.C. §112, second paragraph, as being indefinite. In particular, the Examiner indicated that it was not clear regarding a plurality of reactive functional groups. Applicants have deleted the "plurality" language from the claim. Therefore, Applicants believe that the claim is clear and definite. Applicants respectfully request withdrawal of the rejection of claim 29 under 35 U.S.C. §112, second paragraph, as being indefinite.

Rejections Over Cahalan et al.

The Examiner rejected claims 25 and 28 under 35 U.S.C. §102(b) as being anticipated by U.S. Patent 5,308,641 to Cahalan et al. (the Cahalan patent). The Examiner cited the Cahalan patent for disclosing human or animal tissue and growth factors. Applicants have amended claim 25 to clarify its scope. Applicants respectfully request reconsideration of the rejection based on the following comments.

In response to Applicants' arguments that Cahalan does not disclose a crosslinked network, the Examiner asserted that the claims did not inherently require a crosslinked network. Applicants have clarified the scope of claim 25 with respect to specifying that the tissue is fully crosslinked. In addition, the Examiner asserts that the "light crosslinking" is only a preferred embodiment in the Cahalan patent. Applicants believe this is a misunderstanding. The **dilute concentration** of the crosslinking agent is preferred in the Cahalan patent, while the light crosslinking is described as an aspect of reaching their objective of linking a biomolecule to the substrate. See, column 4, line 66 to column 5, line 3.

The Examiner further asserts that the polyalkylimine crosslinks the tissue. The basis for this statement is not known. **Polyimides,** not **polyimines**, are known to crosslink tissue. The Cahalan patent acknowledges that the substrate may have to be activated with aldehyde groups to bind the polyalkylimines. See column 5, lines 11-16. Since activation of the tissue may be required to bind polyalkylimines, the Cahalan patent does not teach how to effectively crosslink tissue with polyalkylimines. Similarly, the Cahalan patent does not provide motivation for crosslinking tissue with polyalkylimines.

The Cahalan patent does not teach or suggest fully crosslinked tissue. Therefore, the Cahalan patent does not anticipate Applicants' claimed invention. Applicants respectfully request withdrawal of the rejection of claims 25 and 28 under 35 U.S.C. §102(b) as being anticipated by the Cahalan patent.

Rejection Under 35 U.S.C. §102(b) Over Bayne et al.

The Examiner rejected claims 25 and 26 under 35 U.S.C. §102(b) as being anticipated by European Patent Application 0476983 to Bayne et al. (the Bayne EP application). The Examiner asserts that the Bayne EP application discloses applying VEGF II to fixed tissue. Applicants believe that this is a misunderstanding of the Bayne EP application. Applicants respectfully request reconsideration of the rejection based on the following comments.

The Examiner correctly notes on page 6 of the Office Action that the Bayne EP application discloses two embodiments. The Examiner also correctly notes that the first embodiment involves application of cells and that the second embodiment involves application of VEGF II. However, the Bayne EP patent only discloses fixed tissue with respect to the first embodiment, not the second embodiment. Since the Bayne EP patent does not disclose fixed tissue with respect to the second embodiment, the Bayne EP application does not anticipate Applicants' claimed invention. Applicants respectfully request withdrawal of the rejection of claims 25 and 26 under 35 U.S.C. §102(b) as being anticipated by the Bayne EP application.

Rejections Over Bayne et al. and Wadstrom

The Examiner rejected claims 1, 2, 4, 5, 9-11 and 29 under 35 U.S.C. §103(a) as being unpatentable over the Bayne EP application in view of U.S. Patent 5,631,011 to Wadström (the Wadström patent). The Examiner cited the Bayne EP application for disclosing an implant with applied fibrin and VEGF II growth factor. The Examiner cited the Wadström patent for disclosing that fibrin is a common biologic glue. However, Applicants believe that there has been a misunderstanding regarding the nature of fibrin. Applicants respectfully request reconsideration of the rejection based on the following comments.

Applicants previously noted that fibrin itself is not an adhesive. Fibrin is a polymerized peptide that forms blood clots. Fibrin monomers are an adhesive during the polymerization process. The Examiner counters that the Bayne EP application discloses that

fibrin can be used as an aid in the attachment of cells. However, this observation in the Bayne EP application is based on the adhesive properties of **cells**, which anchor to an appropriate substrate, **not** on the adhesive properties of the fibrin. As noted in Applicants' specification at page 19, lines 3-6, cells can express adhesion proteins. Fibrin is an appropriate substrate for cells to bind to. Applicants' claims are directed to anchoring of a growth factor with a biologic adhesive, not on the anchoring of cells. The Bayne EP application does not teach or suggest a biologic adhesive for the association of a polypeptide growth factor. The disclosure in the Wadström patent does not disclose polymerized fibrin as a suitable adhesive for a polypeptide growth factor.

Since the combined disclosures of the Bayne EP application and the Wadström patent do not teach or suggest a biologic adhesive for associating a polypeptide growth factor with a tissue, the combined disclosures of the cited references do not render Applicants' claims prima facie obvious. Applicants respectfully request withdrawal of the rejection of claims 1, 2, 4, 5, 9-11 and 29 under 35 U.S.C. §103(a) as being unpatentable over the Bayne EP application in view of the Wadström patent.

Rejections Under 35 U.S.C. 103(a) Over Bayne et al., Wadström and Carpentier et al.

The Examiner rejected claims 6-8, 14, 15, 21-24, 27 and 28 under 35 U.S.C. §103(a) as being unpatentable over the Bayne EP application and the Wadström patent as applied to claims 1-5, 9-11 and 29, and further in view of U.S. Patent 4,648,881 to Carpentier et al. (the Carpentier patent). The Examiner cited the Carpentier patent for disclosing uncrosslinked and crosslinked tissue, a heart valve form of the tissue and other tissue types. The Examiner asserted that it would have been obvious to use these materials as the substrates within the teachings of the Bayne EP application for the applications contemplated by Carpentier. Applicants respectfully request reconsideration of the rejections based on the following comments.

The deficiencies of the Bayne EP application and the Wadström patent are described above with respect to claims 1 and 25. The independent claim groups are discussed separately.

With respect to claims 6-8, which depend from claim 1, the Bayne EP application and the Wadström patent do not teach or suggest a biologic adhesive that associates a polypeptide growth factor to tissue. The Carpentier patent does not teach or suggest biologic adhesives or polypeptide growth factors. Therefore, the Carpentier patent does not make up for the deficiencies of the Bayne EP application and the Wadström patent. Since none of the cited references teach or suggest the claimed approaches for associating a polypeptide growth factor with tissue, the combined disclosures of the cited references do not render claims 6-8 obvious.

With respect to claims 14, 15 and 21-24, the Examiner acknowledged that the Bayne EP application does not disclose a valve structure, as claimed by Applicants. While the Carpentier patent discloses tissue-based heart valves, the motivation to combine the disclosure of the Carpentier patent with the disclosures of the Bayne EP patent and the Wadström patent as suggested by the Examiner is unclear. Furthermore, the combined disclosures of the cited references do not provide a reasonable expectation of success.

The Bayne EP application discloses two embodiments for treating blood vessels, one involving cultured cells and a second involving coating of artificial vessels. There is no teaching, suggestion or motivation to apply these techniques to valved prostheses. The Carpentier patent describes the processing of tissue to form heart valves to reduce the incidence of calcification. The Carpentier patent does not teach, suggest or motivate the use of growth factors since it is unclear what further processing is consistent with valve function and avoidance of calcification. The Wadström patent does not teach or suggest valved prostheses. Therefore, there is no motivation provided by the references to combine the disclosure of the Carpentier patent with the disclosures of the Bayne EP application and the Wadström patent.

Furthermore, the Carpentier patent discloses various treatments, such as treatment with metal ions, to reduce calcification. It is unclear how these treatments would interact with the growth factors. As amended, Applicants' claims indicate that the growth factor is effective to stimulate affiliation with viable cells. Since the interaction is unclear between the processing described in the Carpentier patent and the application of growth factors as described in the Bayne EP application, the combined disclosures of the cited references do not provide a reasonable expectation of success with respect to the claimed invention. The Bayne EP application does not seem to describe evaluation of the effectiveness of the VEGF for promoting association of viable cells with a substrate. Since the references do not motivate the combination with respect to Applicants' claimed invention and since the combined disclosures do not provide a reasonable expectation of success, the combined disclosures of the Bayne EP application, the Wadström patent and the Carpentier patent do not render claims 14, 15 and 21-24 obvious.

With respect to claims 27 and 28, which depend from claim 25, the Bayne EP application and the Wadström patent do not teach or suggest association of a polypeptide growth factor with fixed/crosslinked tissue. The Carpentier patent similarly does not teach or suggest association of a polypeptide growth factor with fixed/crosslinked tissue. Since the combined disclosures of the Bayne EP application, the Wadström patent and the Carpentier patent do not teach or suggest association of a polypeptide growth factor with fixed/crosslinked tissue, the combined disclosures of the cited references do not render claims 27 and 28 obvious.

In view of the above comments, Applicants respectfully request withdrawal of the rejection of claims 6-8, 14, 15, 21-24, 27 and 28 under 35 U.S.C. §103(a) as being unpatentable over the Bayne EP application and the Wadström patent as applied to claims 1-5, 9-11 and 29, and further in view of the Carpentier patent.

## CONCLUSIONS

In view of the foregoing, it is submitted that this application is in condition for allowance. Favorable consideration and prompt allowance of the application are respectfully requested.

The Examiner is invited to telephone the undersigned if the Examiner believes it would be useful to advance prosecution.

Respectfully submitted,

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Peter S. Dardi

ATTACHMENT
REDLINED AMENDMENT

Claims As Amended

Claims 14, 25 and 29 have been amended as follows:

14. (Five Times Amended) A prosthetic heart valve comprising a substrate with associated VEGF, wherein said VEGF is associated with the substrate by direct attachment, a biologic adhesive, covalent bonding using crosslinking agents, antibody-antigen associations, specific binding protein-receptor associations or enzyme-substrate associations, the prosthesis having a valve structure, said polypeptide growth factors being effective to stimulate the affiliation of viable cells with said substrate.

25. (Amended) A prosthesis comprising fully crosslinked tissue having an exogenous polypeptide growth factor associated therewith.

29. (Twice Amended) A prosthesis for a human patient comprising allograft or xenograft tissue having a polypeptide growth factor associated therewith by a biologic adhesive, covalent bonding using crosslinking agents comprising [a plurality of] reactive functional groups, antibody-antigen associations, specific binding protein-receptor associations or enzyme substrate associations, said polypeptide growth factors being effective to stimulate the affiliation of viable cells with said tissue.